

PATENT #15

## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Bergnes et al.

Attorney Docket No.: CYTOP009C5

Application No.: 09/724,897

Examiner: Truong, Tamthom Ngo

Filed: November 28, 2000

Group: 1624

Title: METHODS AND COMPOSITIONS  
UTILIZING QUINAZOLINONESCommissioner for Patents  
Washington, D.C. 20231

TECH CENTER 1600/2900

OCT 4 2002

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DECLARATION OF GUSTAVE BERGNES, Ph.D.  
UNDER 37 C.F.R. § 1.132

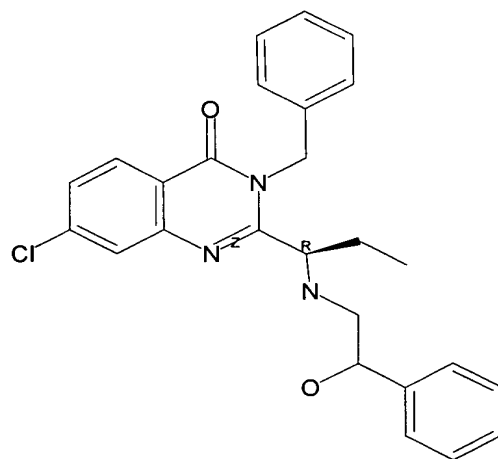
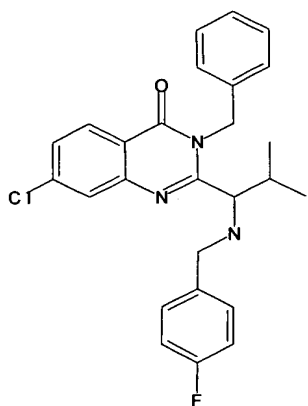
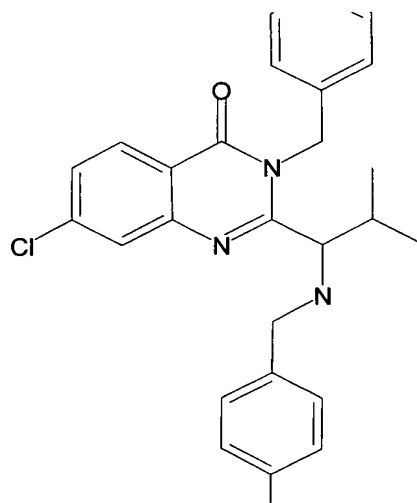
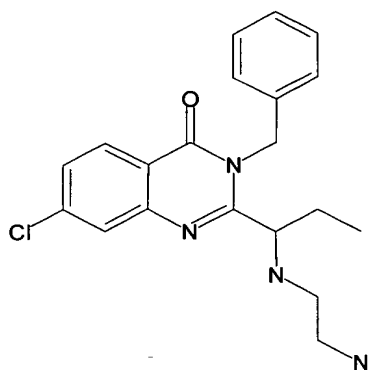
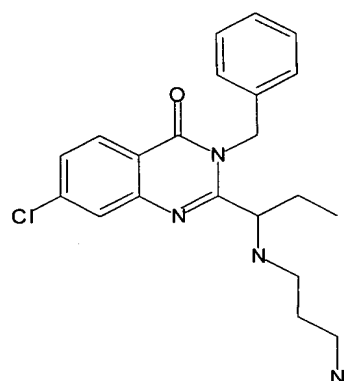
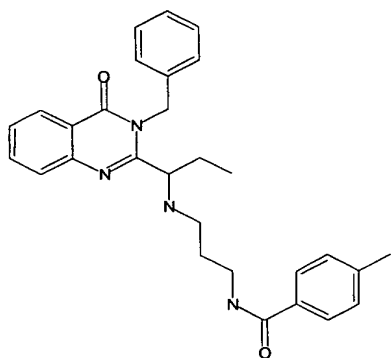
Sir:

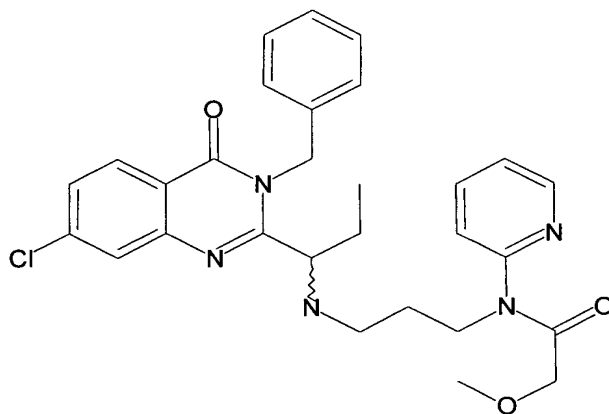
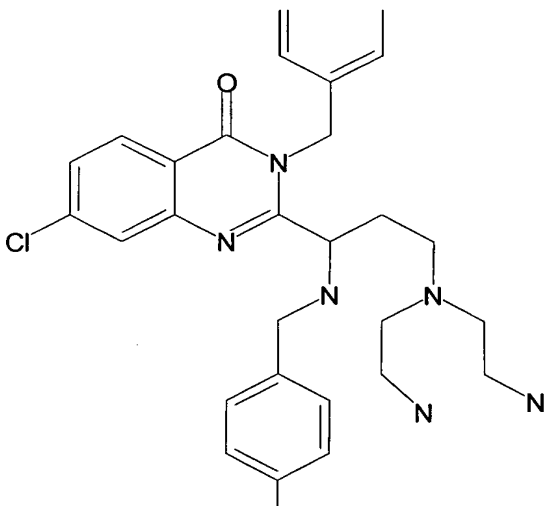
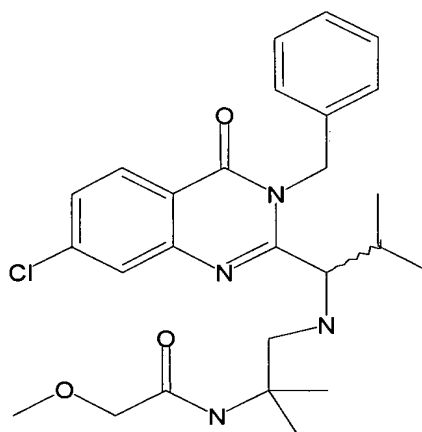
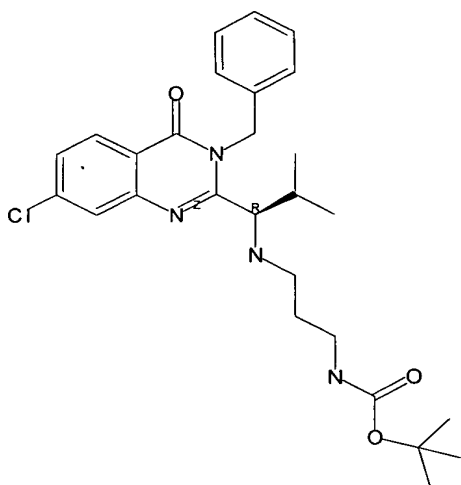
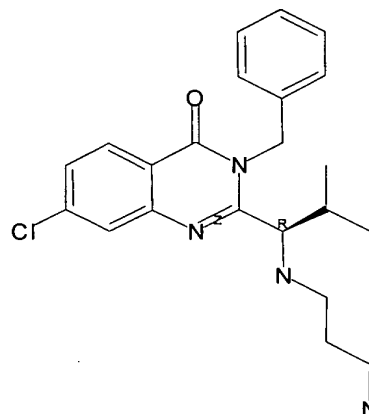
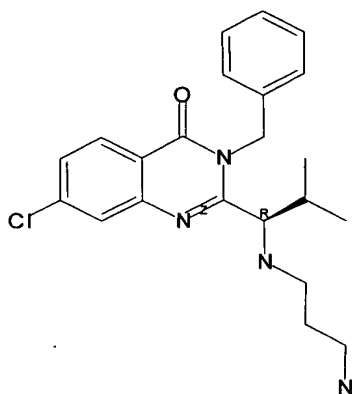
1. I, Gustave Bergnes, am a co-inventor of the subject matter embodied in the above-identified patent application.
2. I am familiar with the Office Action from the United States Patent and Trademark Office mailed March 22, 2002, in the above-named application.
3. In the Office Action, the Examiner rejects Claims 31, 50, 51, and 56, under 35 U.S.C. §112, first paragraph, as the specification, while being enabling for the preparation of the claimed compounds, does not reasonably provide enablement for the use of the compounds. The Examiner further argues that one skilled in the art would have to carry out undue experimentation to find out if the claimed compounds can inhibit mitotic kinesin KSP, and at what dosage.
5. Various assays to determine the activity of the quinazolinone compounds are exemplified in the Specification at pages 44-48. These assays include the induction of mitotic arrest in a cell population treated with the compound; monopolar spindle formation following application of a quinazolinone KSP inhibitor; and inhibition of cellular proliferation in tumor cell lines treated with quinazolinone KSP inhibitors. Other assays are described at pages 18-23.
6. One specific measure of inhibition that is discussed in the subject application is  $K_i$  or the dissociation rate constant for the interaction of the quinazolinone compound with the kinesin KSP. See, Specification at page 22. The  $K_i$  for a compound also can be determined from the

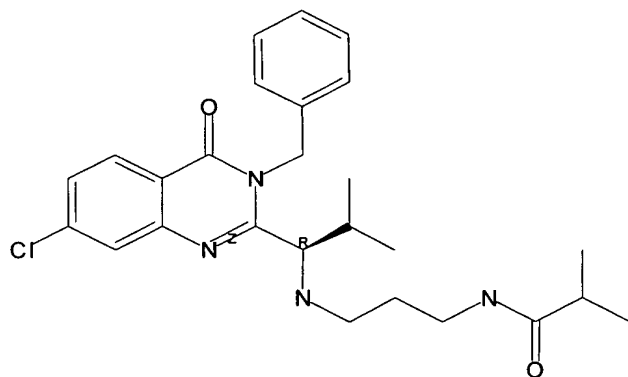
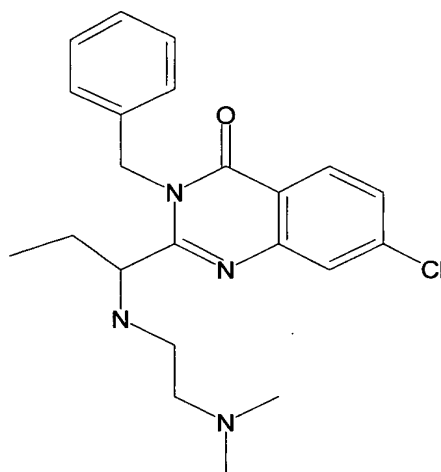
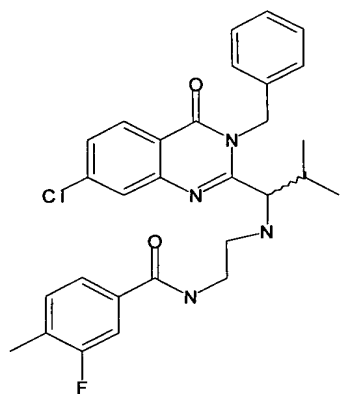
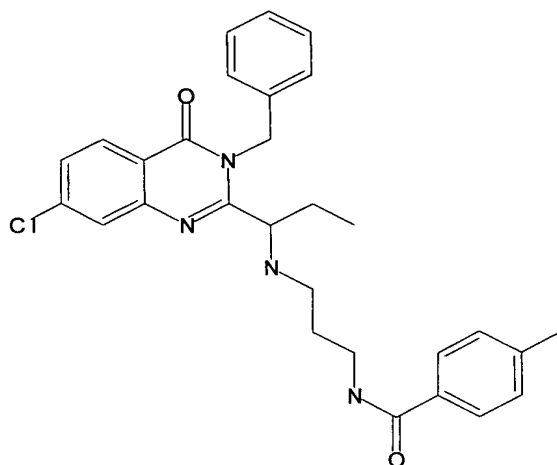
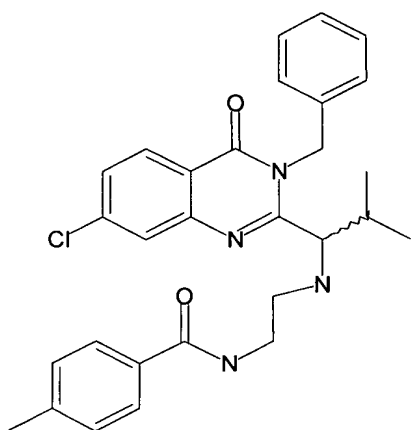
IC<sub>50</sub> of that compound. See, Specification at page 22. Experimental procedures for determining IC<sub>50</sub>'s are given in the Specification at pages 46 and 47.

7. The Specification further states that preferred compounds have K<sub>i</sub>'s of less than about 100 μM. See, Specification at page 22. Specific compounds having K<sub>i</sub>'s in this range are shown, for example, on page 42.

8. Using the procedures set forth in the specification, the K<sub>i</sub> and/or IC<sub>50</sub>'s of the following quinazolinone compounds were determined:







9. Each of the above compounds had a  $K_i$  of less than about 100  $\mu$ M.

10. Compounds encompassed by the present claims have been demonstrated to inhibit both KSP activity and cellular proliferation. Given this correlation and the magnitude of the  $K_i$ 's of the above compounds, I believe that a skilled person in the field would understand that the above compounds as well as others encompassed by the present claims should have the effect of inhibiting KSP activity and be useful in treating a disorder associated with KSP kinesin activity and/or cellular proliferative diseases.

The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

Dated: 9/12/02

Signed:   
GUSTAVE BERGNES, Ph.D.